

US009510569B2

(12) United States Patent

Economides et al.

(54) GENETICALLY MODIFIED MOUSE WITH AN INDUCIBLE ACVRI GENE WITH A MUTANT R206H EXON 5 THAT HAS ECTOPIC BONE FORMATION

(71) Applicant: **REGENERON**

PHARMACEUTICALS, INC.,

Tarrytown, NY (US)

(72) Inventors: Aris N. Economides, Tarrytown, NY

(US); Sarah Jane Hatsell, Nyack, NY

(US)

(73) Assignee: Regeneron Pharmaceuticals, Inc.,

Tarrytown, NY (US)

(*) Notice: Subject to any disclaimer, the term of this

patent is extended or adjusted under 35

U.S.C. 154(b) by 0 days.

(21) Appl. No.: 14/207,320

(22) Filed: Mar. 12, 2014

(65) **Prior Publication Data**

US 2014/0283158 A1 Sep. 18, 2014

Related U.S. Application Data

- (60) Provisional application No. 61/778,814, filed on Mar. 13, 2013.
- (51) Int. Cl.

 A01K 67/027
 (2006.01)

 C07K 14/71
 (2006.01)

 C12N 15/85
 (2006.01)

(52) U.S. Cl.

CPC A01K 67/0275 (2013.01); A01K 2217/072 (2013.01); A01K 2217/203 (2013.01); A01K 2227/105 (2013.01); A01K 2267/0306 (2013.01); C07K 14/71 (2013.01); C12N 2015/8536 (2013.01); C12N 2800/30 (2013.01)

(10) Patent No.: US 9,510,569 B2

(45) **Date of Patent:**

Dec. 6, 2016

(58) Field of Classification Search

(56) References Cited

U.S. PATENT DOCUMENTS

7,205,148 B2 * 4/2007 Economides et al. 435/462 2006/0179501 A1 * 8/2006 Chan et al. 800/18

FOREIGN PATENT DOCUMENTS

WO WO 02/088353 A2 7/2002 WO WO 02/088353 A3 7/2002 WO WO 2007/123896 A2 11/2007 (Continued)

OTHER PUBLICATIONS

Yu (Nature Med., Dec. 2008, vol. 14, No. 12, p. 1363-1369).*
(Continued)

Primary Examiner — Michael Wilson (74) Attorney, Agent, or Firm — Neil Miyamoto; Alston & Bird LLP

(57) ABSTRACT

A genetically modified mouse is provided that comprises a conditional Acvr1 allele that comprises a mutated exon that, upon induction, converts to a mutant exon phenotype, wherein the mutant exon phenotype includes ectopic bone formation. Mice comprising a mutant Acvr1 exon 5 in antisense orientation, flanked by site-specific recombinase recognition sites, are provided, wherein the mice further comprise a site-specific recombinase that recognizes the site-specific recombinase recognitions sites, wherein the recombinase is induced upon exposure of the mouse to tamoxifen. Upon exposure to tamoxifen, the recombinase is expressed and acts on the RRS-flanked mutant exon 5 and places the mutant exon 5 in sense orientation and deletes the wild-type exon.

4 Claims, 12 Drawing Sheets

